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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,092	05/18/99	PAULISTA M	P564-9010

EXAMINER	
KAUSHAL S	
ART UNIT	**PAPER NUMBER**
1633	17

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DATE MAILED: 09/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/297,092	Applicant(s) PAULISTA ET AL.	
	Examiner Sumesh Kaushal	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 05/17/01 have been fully considered but is found unpersuasive for the same reasons of record as set forth in the official action mailed on 01/17/01.

Claims 14-16 are canceled by the applicant. Claims 17, 21, 24-26 and 28-29 are amended. Claims 17-29 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

The applicant collectively argued the Written description and Enablement rejections in the response filed on 05/17/01 (pages 4-6).

Claims 28-29 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**, for the same reasons of record as set forth in the official action mailed on 01/17/01.

Claims 17-29 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an implant material comprising a bioactive material composed of calcium phosphate and MP52 protein or DNA encoding MP52, does not reasonably provide enablement for an implant material comprising a bioactive matrix material composed of calcium phosphate and any and all cartilage-inducing and/or bone inducing protein or DNA encoding the protein, such that the protein is a differs form SEQ ID NO:1, homodimer of SEQ

ID NO:1 or a related protein, dimer of another protein of TGF-β superfamily and/or a protien use that uses same receptor mechanism of proteins claimed above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the official action mailed on 01/17/01.

The applicant collectively argued the Written description and Enablement rejection in the response filed on 05/17/01 (pages 4-6). The applicant argues that the invention as claimed encompass SEQ ID NO:1. The applicant argues that the specification teaches proteins are preferably included which have same receptor mechanism and/or the same signal transmission as the membrane of BMP and/or GDF family in particular MP52. The applicant further argues that GDF-5 binding profile corresponds to MP52 receptors (response: page 6, ¶1).

However, this is not found persuasive because the invention as claimed encompass any and all proteins that differ from SEQ ID NO:1 and are derived from any and all vertebrates, dimers of any and all proteins of TGF-β superfamily, and any and all protiens that uses same receptor mechanism. At best the specification only teaches SEQ ID NO:1 which encodes MP52 protein. The earlier office action clearly states that disclosure fails to describe the common attributes or characteristics that identify members of the genus, such as which specific protein domains confer cartilage and bone-inducing ability, and because the genus is highly variant, the ability to induce cartilage or bone growth is insufficient to describe the genus. Additionally, the applicant fails to point out where in the specification is support for the claimed genus which encompass any and all proteins that differ from SEQ ID NO:1 and are derived from any and all vertebrates, dimers of any and all proteins of TGF-β superfamily, and any and all protiens that uses same receptor mechanism. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

In addition it is unclear how one skill in the art would use the invention as claimed without any reasonable expectation of success in view of arguments above. The earlier office action clearly states that the specification discloses by incorporation by reference members of the TGF-β superfamily (pg 1, para. 2-pg 4, para. 1), but fails to disclose fragments, portions, or heterodimers of said members, or non-human homologues to SEQ ID NO: 1, which have demonstrated the ability to induce cartilage and/or bone growth. Neither is it widely known in the art which specific domains and sequences of the members of the TGF-β superfamily possesses such properties. Therefore, the lack of guidance on the coding sequence of specific fragments, portions, or heterodimers, or non-human homologues of SEQ ID NO: 1, would have required a tremendous amount of experimenation by the skilled artisan to ascertain said sequences such that their incorporation into a matrix would result in any cartilage or bone induction in vivo. Furthermore, the specification fails to teach the delivery nucleic acid as claimed would result in the therapeutic expression of a protein (as claimed) that promotes cartilage and/or bone growth in vivo. Therefore, the specification does not disclose which fragments or portions of protein or DNA sequences, or fusion proteins of the TGF-β superfamily would induce cartilage and/or bone growth in vivo, nor is such widely known in the art. Therefore, one of skill in the art would have to practice undue experimentation to determine which sequences from a TGF-β superfamily would meet this functional limitation.

Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites the limitation "the first component" and "the second component" in line 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 21 recites the limitation "the first component" and "the second component" in line 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "the second component" and "the first component" in line 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "the same receptor mechanism" in section (e). There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 17-29 remain rejected under 35 USC 103 as being obvious over Urist et al. in view of Opperman et al, Yan et al, Fujino et al and Hoetten et al for the same reasons of record as set forth in the official action mailed on 01/17/01.

The applicant argues that after the amendment the rejection has been rendered moot (response: page 6, ¶3). However, this is not found persuasive because the scope of claims encompass an implant material which comprising a bioactive matrix material composed of calcium phosphate and, any and all cartilage-inducing and/or bone inducing protein or DNA encoding the protein, such that the protein is a differs form SEQ ID NO:1, homodimer of SEQ ID NO:1 or a related protein, dimer of another protein of TGF-β superfamily and/or a protien use that uses same receptor mechanism of SEQ ID NO:1 and/or a protein that differs from SEQ ID NO:1.

The office action mailed on 04/26/00 cleearly states that Urist, MR teaches the use of a biodegradable porous beta tricalcium phosphate ceramic matrix with bone morphogenetic protein (BMP) (col 2, lines 35-44) for the slow release of said protein for the purpose of inducing new bone growth (abstract). Urist, MR also teaches a method of making said matrix with BMP by contacting the porous ceramic with a liquid containing the BMP, then evaporating the solvent through sublimation or freeze drying while entrapping the BMP within the pores of the ceramic (col 3, lines 45-65, & claims 17-18), and leaving the composition in a liquid, hence injectable

form which may be shaped as desired (col 4, lines 13-15). Urist also discloses the use of said matrix for the repair of bone in extraskeletal and intraskeletal sites (col 4, lines 40-45). Urist et al do not disclose the use of ethanol precipitation or bioactive materials.

Oppermann et al teach a collagen matrix and a method of making such wherein a recombinantly produced osteogeneic homodimeric proteins such as OP1-16V (claim 2) is interspersed within the pores of the matrix via ethanol precipitation (pg 51, para 1) and released from the matrix in a sustained release manner (pg 44, para 4). Said matrix is utilized for the repair of orthopedic, periodontal, and reconstructive procedures (pg 44, para 4).

Yan et al disclose that materials comprising predominantly tricalcium phosphate are bioactive, as demonstrated by their ability to induce bone growth *in vivo*. Yan et al also disclose that said materials are also biocompatible due to their demonstrated low toxicity and low inflammatory response *in vivo* (abstract).

Fujino et al teach the identification of MP52, which has 100% identity to SEQ ID NO: 1. (Accession W11900), and discloses its use in bone induction.

Hoetten et al teach the identification of transforming growth factor differentiation 5, a cartilage-derived morphogenetic protein which has 100% identity to SEQ ID NO: 1 (Accession JC2347), and proposes its use in cartilage growth induction.

In light of Urist, Oppermann, Yan, Hoetten and Fujino et al it would have been obvious to one of ordinary skill in the art to combine the tricalcium phosphate ceramic implant of Urist et al with a TGF-β superfamily protein, such as MP-52 (SEQ ID NO: 1), and to make said implant utilizing ethanol precipitation or sublimation. One would have been motivated to do this to deliver a growth factor in a time release controlled manner to a tissue in need of repair or regeneration of cartilage (Hoetten et al, abstract) or bone (Fujino et al, abstract); and because the use of ethanol precipitation or freeze drying were known standards in the art of forming a matrix with a therapeutic protein (Urist, col 3, lines 45-65, & Oppermann et al, pg 51, para 1). There

would have been a reasonable expectation of success because of Oppermann's et al and Urist's demonstration of the ability to utilize modified growth factors seeded within the pores of a biodegradable matrix to regenerate bone (full patents), while Hoetten teaches that SEQ ID NO: 1 is a growth factor to regenerate cartilage. Therefore, one of ordinary skill in the art would have known that substitution of SEQ ID NO:1 would have resulted in cartilage and/or regrowth enhancement. (It is noted that the pore size and microporosity measured as a percent volume is a result effective variable which one of ordinary skill could modify via methods of solvent precipitation, sintering, and particulate and salt leaching- See Laurencin et al, US Patent 5,866,155, col. 3, line 14-col. 4, line 32). It would also have been obvious to one of ordinary skill in the art to use said implant or composition comprising such to treat a bone or cartilage defect, fracture, or replacement, such as in cosmetic or plastic surgery or in periodontosis. One would have been motivated to use the claimed invention for such because it was routine in the art of tissue engineering at the time of the invention to utilize matrices, such as calcium phosphate or collagen, with growth factors for implantation in vivo to promote the re-growth and differentiation of tissue (Oppermann et al, pg 44, para 4; Urist, col 4, lines 40-45).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED to facilitate further examination.

SUMESH KAUSHAL
PATENT EXAMINER

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER